SYNTHESIS AND ANTICONVULSANT SCREENING OF SOME NOVEL DERIVATIVES OF SUBSTITUTED BENZOFURAN

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Abstract
A series of N-(2-benzoylbenzofuran-3-yl)-4-(substituted)butanamides (IIIa-f) were synthesized in good yield and evaluated for anticonvulsant activity and neurotoxic study. The identity of the synthesized compounds was confirmed on the basis of their elemental analysis and spectral data. In anti-MES test compounds IIIb, IIIc, IIId and IIIf showed potent activity. Compounds IIIa and IIIe were less toxic as compared with the standard drug phenytoin.

Keywords: Benzofuran; Butanamides; Anticonvulsant; Neurotoxic study

1. Introduction
Since the past few decades, the literature has been enriched with progressive findings about the synthesis and pharmacological activities of various substituted benzofuran derivatives. During recent years, there has been intense investigation of different classes of benzofuran compounds and many of them were found to be pharmacologically active. The substituted benzofurans have attracted much attention due to their prominent utilization as antimicrobial1-2, anti-inflammatory3-4, anticonvulsant5-6, antitumor7-8, Anti-HIV9, Antidiabetic10 and antitubercular11, activity probably resulting from its planar and compact structure.

Benzofurans, heterocyclic compounds of varied biological activities were found to be one of the new classes of anticonvulsant agents as revealed by literature survey5-6. In recent years, the field of antiepileptic drug development (ADD) has become quite dynamic, affording many promising research opportunities, and there is a continuing demand for new anticonvulsant agents as it has not been possible to control every kind of seizure with currently available antiepileptic drugs.

The amides are a class of compounds presenting a wide range of biological applications and anticonvulsant activity12-14. This prompted us to synthesize and study anticonvulsant activity of compounds incorporating both these moieties i.e., Benzofuran and amides. The compounds were evaluated for their antiepileptic and neurotoxic properties according to the protocols of Antiepileptic Drug Development (ADD) program developed by National Institute of Health (NIH).

2. Materials and methods
2.1 Chemistry: The melting points were determined in open glass capillary using kjeldahl flask containing liquid paraffin and are uncorrected. NMR spectra were recorded on Bruker model DRX-300 NMR spectrometer (chemical shift in ppm) in CDCl3/DMSO-d6 using Tetra methyl silane (TMS) as internal reference. Chemical shifts were reported in parts per million (ppm, δ) and the signals were described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Elemental analysis (N) was undertaken with a Perkin-Elmer model analyzer, and all analyses were consistent with theoretical values (within 0.4%) unless indicated. The homogeneity of the compounds was checked by thin layer chromatography (TLC) on silica gel G (Qualigens) coated plates by using Cyclohexane: Ethyl acetate (8:2) as solvent system. Iodine chamber and UV lamp were used for the visualization of TLC spots.

N-(2-benzoylbenzofuran-3-yl)-4-chlorobutanamide (II)
A mixture of 2-Benzoyl-1-benzofuran-3-amines (I) (0.02mol) and 4-chlorobutyryl chloride (5ml) was refluxed on water bath for 30 min. and poured into ice water with stirring. The solid, which separated, was collected and recrystallized from ethanol as colorless needles (II).

N-(2-benzoylbenzofuran-3-yl)-4-(substituted)butanamides (IIIa-f)
To a solution of N-(2-benzoylbenzofuran-3-yl)-4-chlorobutanamide (II, 1 mmol) in dioxane (10 ml), different amines (2 mmol) was added and stirred at room temperature for 24 hr. The reaction mixture was evaporated to dryness. To the residue, water (25 ml) and chloroform (25 ml) was added and the organic layer was separated with the help of separating funnel, after that organic layer (chloroform) was evaporated and the residue obtained is IIIa-f.

The spectral data of (IIIa-f) are given below. The physico-chemical parameters of the synthesized compounds are presented in Table 1.

N-(2-benzoylbenzofuran-3-yl)-4-(4-furan-2-carbonyl)piperazin-1-yl)butanamide (IIIa)

1H NMR (CDCl₃-d6): (δ, ppm) 11.37 (s, 1H, NH), 7.27-8.30 (m, 4H, CH Benzofuran, 5H, Ar-H), 2.35 (t, 2H, COCH₂), 1.77 (m, 2H, CH₂β to CO), 2.47 (t, 2H, CH₂γ to CO), 3.20 (t, 4H, CH₂ of piperazine), 3.63 (t, 3 and 5 CH₂ of piperazine), 8.09 (d, 1H, 2’ CH Pyridinyl), 6.60 (t, 1H, 3’ CH Pyridinyl), 7.56 (t, 1H, 4’ CH Pyridinyl), 6.70 (d, 1H, 4’ CH Pyridinyl)

N-(2-benzoylbenzofuran-3-yl)-4-(4-pyridin-2-y1)piperazin-1-yl)butanamide (IIIb)

1H NMR (CDCl₃-d6): (δ, ppm) 11.38 (s, 1H, NH), 7.28-8.31 (m, 4H, CH Benzofuran, 5H, Ar-H), 2.35 (t, 2H, COCH₂), 1.78 (m, 2H, CH₂β to CO), 2.47 (t, 2H, CH₂γ to CO), 2.46 (t, 2H, CH₂γ to CO), 3.44 (t, 2 and 6 CH₂ of piperazine), 3.63 (t, 3 and 5 CH₂ of piperazine), 8.09 (d, 1H, 2’ CH Pyridinyl), 6.60 (t, 1H, 3’ CH Pyridinyl), 7.56 (t, 1H, 4’ CH Pyridinyl), 6.70 (d, 1H, 4’ CH Pyridinyl)

N-(2-benzoylbenzofuran-3-yl)-4-(dipropylamino)butanamide (IIIc)

1H NMR (CDCl₃-d6): (δ, ppm) 11.40 (s, 1H, NH), 7.27-8.32 (m, 4H, CH Benzofuran, 5H, Ar-H), 2.35 (t, 2H, COCH₂), 1.77 (m, 2H, CH₂β to CO), 2.47 (t, 2H, CH₂γ to CO), 2.46 (m, 4H, N-CH₃ of isopropyl), 1.46 (m, 4H, N-CH₂ CH₃ of isopropyl), 0.90 (t, 6H, CH₃ of isopropyl)

N-(2-benzoylbenzofuran-3-yl)-4-(cyclohexyl(methyl)amino)butanamide (IIId)

1H NMR (CDCl₃-d6): (δ, ppm) 11.29 (s, 1H, NH), 7.26-8.31 (m, 4H, CH Benzofuran, 5H, Ar-H), 2.34 (t, 2H, COCH₂), 1.77 (m, 2H, CH₂β to CO), 2.46 (t, 2H, CH₂γ to CO), 2.25 (s, 3H, N-CH₃), 2.56 (m, 1H), 1’ CH of cyclohexyl), 1.33-1.57 (m, 4H, 2’ & 6’ CH of cyclohexyl), 1.21-1.11 (m, 4H, 3’ & 5’ CH of cyclohexyl), 1.47-1.50 (m, 2H, 4’ CH of cyclohexyl)

N-(2-benzoylbenzofuran-3-yl)-4-(dicyclohexylamino)butanamide (IIIf)

1H NMR (CDCl₃-d6): (δ, ppm) 11.35 (s, 1H, NH), 7.28-8.32 (m, 4H, CH Benzofuran, 5H, Ar-H), 2.35 (t, 2H, COCH₂), 1.77 (m, 2H, CH₂β to CO), 2.46 (t, 2H, CH₂γ to CO), 2.56 (m, 2H, 1’ CH of cyclohexyl), 1.33-1.57 (m, 8H, 2’ & 6’ CH of cyclohexyl), 1.21-1.11 (m, 8H, 3’ & 5’ CH of cyclohexyl), 1.47-1.50 (m, 4H, 4’ CH of cyclohexyl)

2.2 Anticonvulsant screening

In the preliminary screening, each compound was administered as i.p. injection at three dose levels (30, 100 and 300 mg/kg), the anticonvulsant activity was assessed after 30 min and 4 hr. intervals of administration. The anticonvulsant efficacy was evaluated by maximal electroshock-induced seizure (MES) using reported procedure15 and the data are presented in Table 2. Ethical approval was obtained from Integral University, Lucknow, Uttar Pradesh, India Animal Ethics Committee (Reg. No. IU/Pharm/Ph.D./CPCSEA/2009/01).

2.3 Neurotoxicity screen:

Minimal motor impairment was measured in mice by the rotarod test using reported procedure16. The mice were trained to stay on an accelerating rotarod that rotates at 10 revolutions/min. The rod diameter was 3.2 cm. Trained animals were given i.p. injection of the test compounds 30, 100 and 300 mg/kg. Neurological toxicity is defined as the failure of the animal to remain on the rod for 1 min. in each of the trials. All the animal experimental protocols have met with the approval of the Institutional Animal Ethics Committee (IAEC). Data are presented in Table 2.

3. Results

The synthesized compounds (IIIa-f) were initially screened at 30, 100 and 300 mg/kg intraperitoneally in mice for anticonvulsant activity (Table 2). All the compounds exhibit anticonvulsant activity. In the MES test compounds IIId, IIIe, IIIf and IIIi showed activity at 100 mg/kg after 0.5 hr. and 4 hr. On the other hand, compounds IIIa and IIIe showed protection in mice at the dose level of...
100 mg/kg after 0.5 hr. and 4 hr. Compounds IIIa and IIIe were toxic at the dose of 300 mg/kg after 0.5 hr. and 4 hr. Compounds IIIb, IIIc, IIId and IIIf were toxic at the dose of 100 mg/kg after 0.5 hr. and 4 hr. However, compounds IIIa and IIIe were less toxic than Phenytoin (100 mg/kg).

Acknowledgments
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References
Where R = 4-(furan-2-carbonyl)piperazin-1-yl, 4-pyridin-2-yl)piperazin-1-yl, dipropylamino, cyclohexyl(methyl)amino, morpholino and dicyclohexyl amino

Scheme 1. Synthetic pathways for compounds IIIa-f.

Table 1. Physico-chemical parameters of the synthesized compounds (IIIa-f).

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound No.</th>
<th>R</th>
<th>Mol. Formula (Mol.wt.)</th>
<th>°M.P (°C)</th>
<th>Percentage Yield (%)</th>
<th>°Rf value</th>
<th>%N Found (Calc.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>IIIa</td>
<td>N</td>
<td>C_{26}H_{23}N_{3}O_{5}  (485.53)</td>
<td>164-166</td>
<td>72</td>
<td>0.50</td>
<td>8.65 (8.69)</td>
</tr>
<tr>
<td>2.</td>
<td>IIIb</td>
<td>N</td>
<td>C_{26}H_{23}N_{3}O_{3}  (468.55)</td>
<td>118-120</td>
<td>69</td>
<td>0.55</td>
<td>11.96 (11.88)</td>
</tr>
<tr>
<td>3.</td>
<td>IIIc</td>
<td>N</td>
<td>C_{26}H_{23}N_{3}O_{3}  (406.52)</td>
<td>175-177</td>
<td>76</td>
<td>0.58</td>
<td>6.89 (6.95)</td>
</tr>
<tr>
<td>4.</td>
<td>IIId</td>
<td>N</td>
<td>C_{26}H_{23}N_{3}O_{3}  (418.53)</td>
<td>143-145</td>
<td>59</td>
<td>0.56</td>
<td>6.69 (6.62)</td>
</tr>
<tr>
<td>5.</td>
<td>IIIe</td>
<td>N</td>
<td>C_{26}H_{23}N_{3}O_{4}  (392.45)</td>
<td>120-122</td>
<td>66</td>
<td>0.51</td>
<td>7.14 (7.09)</td>
</tr>
<tr>
<td>6.</td>
<td>IIIf</td>
<td>N</td>
<td>C_{26}H_{24}N_{2}O_{4}  (486.65)</td>
<td>187-189</td>
<td>68</td>
<td>0.76</td>
<td>7.87 (7.84)</td>
</tr>
</tbody>
</table>
Melting point of the compounds at their decomposition, Solvent system- Cyclohexane: Ethyl acetate (8:2), Elemental analysis for N was within ±0.4% of the theoretical values.

Table 2: Anticonvulsant and neurotoxicity results of \(N\)-(2-benzoylbenzofuran-3-yl)-4-(substituted) butanamides (IIIa-f)

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>MES screen</th>
<th>Toxicity screen</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0.5 hr</td>
<td>4h</td>
</tr>
<tr>
<td>IIIa</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IIIb</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>IIIc</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>IIId</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>IIIe</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>IIIf</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

Doses of 30, 100 and 300 mg/kg were administered i.p. The figures in the table indicate the minimum dose whereby bioactivity and neurotoxicity was demonstrated in half or more of the mice. The animals were examined 0.5 and 4 hr after injections were made.